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Depression—An Analysis of a Follow-up Study

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The year 1957 heralded a significant advance in the treatment of depressive states. It was then that Loomer *et al.* (1957), and Crane (1957), published their findings on the use of iproniazid, and Kuhn (1957), published his findings on the use of imipramine. Iproniazid was the first of a series of monoamine oxidase inhibitors which were rapidly developed and used in the treatment of depressive states. In the last few years, their use, especially in "endogenous" depression, has been eclipsed by the iminodibenzyl derivatives; first imipramine, then amitriptyline and later the demethylated derivatives, desipramine and nortriptyline. However, the later monoamine oxidase inhibitors are still widely used, especially in "reactive" depression and some neurotic states.

The iminodibenzyl derivatives have found a wider application in a variety of general medical conditions, such as cardiovascular disorders, psoriasis, bronchial asthma, diabetes mellitus (Kaplan *et al.*, 1962), manic states and narcolepsy (Akimoto *et al.*, 1962; Schou, 1963) and minor criminal sexual compulsions (Goldner, 1962). Despite the considerable literature on these drugs, there are still no generally accepted criteria for their use. The very rapidity with which they have followed each other has militated against this. Pharmacological and physiological characteristics have been described (Fink, 1959; Sigg, 1959; Vernier, 1961; Akimoto *et al.*, 1962; Himwich *et al.*, 1962; Rathbun and Slater, 1963), and there have been numerous drug trials, both controlled and uncontrolled.

One of the most disappointing features has been the lack of the follow-up studies which are necessary to provide further information on the natural history of the depressive states and on the comparative value of the drugs on a long term basis.

One of the most detailed and extensive comparisons of imipramine and amitriptyline was reported by Burt *et al.* (1962), and Hordern *et al.* (1963). This paper reports the follow-up of these same patients eighteen months after their discharge from hospital.

Summary and Results of Original Investigations

Burt *et al.* (1962), and Hordern *et al.* (1963), reported a double-blind comparison of imipramine and amitriptyline in a sample of 137 female patients who were admitted to a psychiatric hospital with a diagnosis of primary depressive illness. Each patient was assessed on the Hamilton rating scale (Hamilton, 1960) on admission, after one week, after four weeks and if necessary after six weeks on the drug. After one month of treatment, if symptom-free, the patients were discharged on a maintenance dosage of 100 mgms. daily for six months; if the condition was basically unchanged they were given E.C.T.; if there was some improvement, they remained on the full dosage for a further two weeks.

Conclusions included the following:

(1) Using discharge without E.C.T. as the criterion of success, amitriptyline, which relieved 81 per cent. of patients, was superior to imipramine, which relieved 54 per cent. ($p < \cdot 002$).

(2) The severity of the individual symptoms did not affect the outlook with amitriptyline; but with imipramine, severity in either depressed mood, reduction of work and interests, agitation, psychic anxiety and retardation was associated with a significantly larger proportion receiving E.C.T.

(3) Endogenous depressives over 50 years of age did significantly better with amitriptyline, though reactive cases did well on both drugs.

(4) The response to one week of treatment, in terms of improvement in Hamilton scale scores, was found to be significantly correlated in the case of amitriptyline with the final outcome. After one week, non-responders could be differentiated by their failure to improve on three symptoms: anorexia, middle insomnia, and reduced work and interests.

Methodology of Present Investigation

It was found possible to follow up 116 of the 137 female patients in the original study. Of the remainder, 5 had died and 16 could not be contacted; these included 9 amitriptyline and 5 imipramine responders and 7 drug non-responders. Table I shows the composition of the 116 cases who were contacted.

TABLE I

Composition of Patients

Amitriptyline responders	47
Imipramine responders	32
Drug non-responders (E.C.T.)	37

The drug responders were maintained on their drug for six months after discharge and followed up at the out-patient clinic, as also were the non-responders. Eighteen months after each was discharged, one of the authors (A.K.) obtained the relevant information from the case histories, which contained information on in- and out-patient contacts with the Department of Mental Health in Victoria. Further data were obtained either by personal interview, interview with a social worker, telephone interview or from a questionnaire posted to the patients. For all but three patients, part at least of the information could therefore be checked. These three, for whom the only source of information was the case histories, had spent nearly all the preceeding eighteen months under the care of the Department.

The study was conducted on a blind basis, in that the author (A.K.) who interviewed the patients and collated all the case material did not know which drug each patient had been given.

Table II shows the distribution of sources of information about the patients.

TABLE II

Sources of Information

Source	Number	Number
Case history	116	
Psychiatric history		64
Telephone interview		12
Social worker interview		13
Questionnaire		24
Case history only		3
TOTAL	116	116

For the purpose of this study the terms "recurrence" and "re-admission" have specific meanings. Recurrence refers to any episode of depression lasting longer than three days, whether treated or untreated (including re-admissions). This criterion of three days was chosen in order to include as many pathological episodes as possible and exclude non-pathological mood swings. Re-admission refers to any admission for depression to one of the Department's mental hospitals, the psychiatric ward of a general hospital, or a private hospital. The categories reactive and endogenous were assigned in the original investigation in terms of historical and phenomenological criteria and not according to the severity of the illness.

RESULTS

The results of the study are presented under three headings: the history of the patients subsequent to discharge, the relative efficacy of the two drugs, and prognostic factors associated with their use.

History Subsequent to Discharge

The analysis of data in this section was made in terms of rates of recurrence and re-admission determined for 6, 12 and 18 months after discharge.

(*a*) *Recurrence Rates*

The rates of recurrence over 6, 12 and 18 months after discharge from hospital are shown

TABLE III

Number and Percentage of Patients with a Recurrence of Depressive Illness
(the number in brackets are the total number in each group)

Group	Drug Responders						Non-Responders (E.C.T.)		
	Amitriptyline			Imipramine					
Time after discharge	6 months	12 months	18 months	6 months	12 months	18 months	6 months	12 months	18 months
Number of patients ..	9 (47)	23 (47)	29 (47)	5 (32)	15 (32)	18 (32)	12 (37)	20 (37)	21 (37)
Percentage	19%	49%	62%	16%	47%	56%	42%	54%	57%

in Table III for responders to each of the drugs and for non-responders.

None of the differences between the groups were statistically significant. There was a suggestion that in the earlier months there might be a difference in favour of the responders, but by 18 months this vanishes, and even at 6 months it was not statistically significant ($p = 0 \cdot 1$).

Jarvie (1954), reported that 71 patients who received E.C.T. and were discharged as recovered had a 35 per cent. relapse rate in three years, but inadequate information was available from 7 patients, and 9 who had "unstable episodes of short duration" were not included in the relapsed group. Kiloh *et al.* (1962), found that of 97 patients treated with imipramine, 58 per cent. responded and remained well for six months as against our figure of 47 per cent.

Fig. 1 demonstrates the recurrence rates for responders and non-responders when separated into reactive and endogenous categories. For the endogenous patients, a higher recurrence rate was indicated for the non-responders, significant at 12 months ($p = \cdot 05$). On the other hand, among the reactive patients, the non-responders showed a lower recurrence rate. The differences were not significant ($p = \cdot 19$ and $\cdot 07$ at twelve and eighteen months respectively).

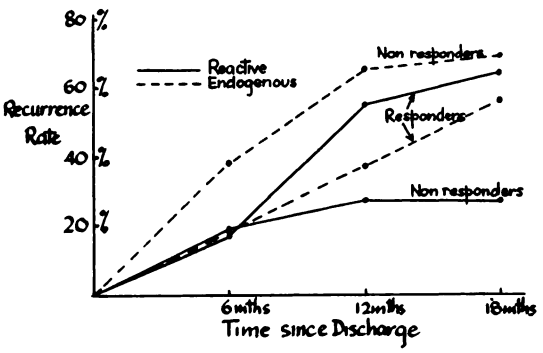

FIG. 1.—Recurrence Rates according to Type of Illness and Outcome of Treatment.

Table IV demonstrates the rates of recurrence over eighteen months for all patients (responders and non-responders included together) when they were separated into the reactive and endogenous categories.

It can be seen that the rates of recurrence for the two categories were very similar despite the

TABLE IV

Total Recurrence Rates for the Reactive and Endogeneous Categories
(the numbers in brackets are the total number in each group)

Category	Reactive			Endogeneous		
Time after discharge ..	6 months	12 months	18 months	6 months	12 months	18 months
Number of patients ..	8 (47)	23 (47)	26 (47)	18 (69)	33 (69)	42 (69)
Percentage	17%	49%	55%	26%	48%	61%

TABLE V

Total Recurrence Rates of the Endogeneous and Reactive Categories for Amitriptyline-Treated Patients
(the numbers in brackets are the total number in each group)

Category	Reactive			Endogeneous		
Time after discharge ..	6 months	12 months	18 months	6 months	12 months	18 months
Number of patients ..	5 (22)	12 (22)	14 (22)	9 (36)	20 (36)	24 (36)
Percentage	23%	55%	64%	25%	56%	67%

TABLE VI

Number and Percentage of Patients with Re-admissions
(the numbers in brackets are the total number in each group)

Group	Drug responders				Non-responders (E.C.T.)	
	Amitriptyline		Imipramine			
Time after discharge ..	12 months	18 months	12 months	18 months	12 months	18 months
Number of patients ..	9 (47)	14 (47)	4 (32)	6 (32)	17 (37)	18 (37)
Percentage	19%	30%	13%	19%	46%	49%

apparent differences shown at twelve and eighteen months in Fig. 1 (n = only 11 for the reactive responders).

It was found that the similarity of the recurrence patterns of the endogenous and reactive categories shown in Table IV was independent of the particular drug used. Table V shows the rates of recurrence of the two categories for the amitriptyline-treated patients alone, and again demonstrates the similar rates of recurrence of the endogenous and reactive categories.

(*b*) *Re-admission Rates*

Re-admission rates for the responders to the two drugs and for the non-responders are shown in Table VI.

There were no significant differences for the responder groups, but the combined responders showed significantly lower re-admission rates than did the non-responder group (Fig. 2). At twelve months $p < \cdot 01$; at eighteen months $p < \cdot 02$.

Only five of the responders (6·3 per cent.), as against ten of the non-responder group (27 per cent.), had more than one re-admission over eighteen months; this difference is highly significant ($p < \cdot 01$).

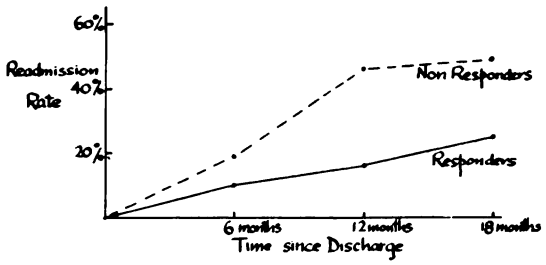

FIG. 2.—Re-admission Rates for Responders and Non-Responders.

In summary, the data presented so far show that during the 18 months after discharge more than half of the drug non-responder group had had at least one recurrence, approximately half had required re-admission, and a quarter had been re-admitted more than once, whilst of the responders three-fifths had had a recurrence, but only about a quarter had been re-admitted once, and one in sixteen had had more than one

re-admission. Angst (1961), found that his group of endogenous depressives treated with imipramine had a six-month re-admission rate of 32 per cent. (based on the 33 original responders), whilst our comparable group had a re-admission rate of 20 per cent. over the same period. Oltman and Friedman (1962), found a re-admission rate of 21 per cent. by two years for their depressives treated with drugs. For depressives treated with E.C.T., Karagulla (1950) found a twelve-month re-admission rate for females of 18·9 per cent. (ours was 16 per cent. for drug-treated patients). Huston and Locher's (1948) figure for the same period was 8 per cent., but not all of the patients were followed up for the same period. Thomas (1954), found a twelve-month recurrence rate of 23 per cent., including re-admissions, those requiring E.C.T., suicides and those who had leucotomies.

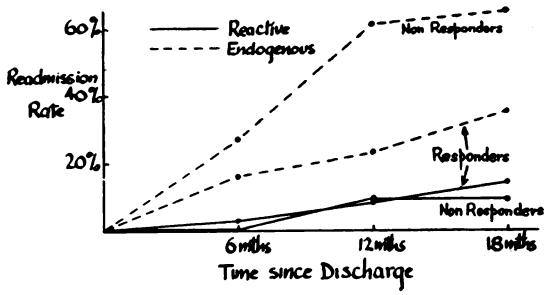

FIG. 3.—Re-admission Rates according to Type of Illness and Outcome of Treatment.

Fig. 3 shows the re-admission rates separately for reactive and endogenous patients. It indicates that the higher rate for non-responders applied only to endogenous patients, and that reactive patients whether responders or non-responders had a low re-admission rate. The differences between the endogenous responders and non-responders by 12 and 18 months were significant (at twelve months $p < \cdot 01$; at eighteen months $p < \cdot 05$).

Fig. 4 shows that the endogenous patients as a group had statistically significantly higher re-admission rates over 6, 12 and 18 months ($p < \cdot 01$, $< \cdot 001$ and $< \cdot 001$ respectively). It can be seen that the re-admission rates were of

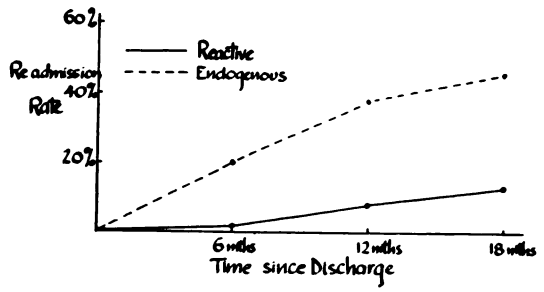

FIG. 4.—Total Re-admission Rates for Reactive and Endogeneous Patients.

the same order for each of the three six-month periods of the follow-up. Calculations of re-admission rates separately for the two drug groups were made, which showed that re-admission patterns were independent of the drug used.

Comparative Efficacy of the Drugs

Hordern *et al.* (1963), showed that amitriptyline gave a statistically significantly better response than imipramine after 4 to 6 weeks of treatment. Fig. 5 gives a longitudinal picture of the comparative efficacy of these drugs, in terms of response without recurrence and response without re-admission.

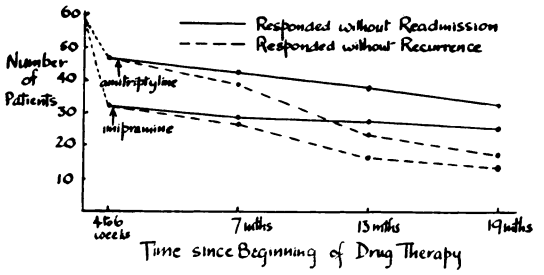

FIG. 5.—The Comparative Efficacy of the Two Drugs in Terms of Re-admissions and Recurrences over the Period of the Original Study and the Follow-up.

Of the 116 patients followed up from the original investigation, 58 had been treated with amitriptyline and 58 with imipramine. After four to six weeks, amitriptyline was markedly superior, 47 amitriptyline and 32 imipramine-treated patients having responded. Eighteen

months after discharge from hospital, 18 amitriptyline responders and 14 imipramine responders had no recurrence, whilst 33 amitriptyline responders and 26 imipramine responders had no re-admissions. The originally better response was still present, but was no longer statistically significant; the earlier superior response to amitriptyline having been partly balanced by the higher rates of recurrence and re-admission of the amitriptyline responders.

Comparison of Drug Responder Groups

Several variables were assessed to elicit any differences in the drug responding groups. The term responder is given a longitudinal meaning and signifies either response without recurrence or response without re-admission 18 months after discharge.

(1) *Age and Type of Illness*

With the criterion of response without re-admission, amitriptyline remained significantly superior only in the "old" (ages 50 to 70 years) endogenous group of patients ($p < \cdot 05$). With the criterion of response without recurrence, there were no significant differences.

(2) *Severity*

No significant differences were found.

(3) *Type of Illness*

There were no significant differences between the drugs for the reactive and endogenous categories after 18 months.

(4) *Psychiatric History*

In terms of response without re-admission, there were no significant differences in drug efficacy in relation to the following variables: the number of previous hospitalizations, the suddenness of onset of the first illness, the speed of onset of the current illness and the number of years since the first hospitalization.

Amitriptyline did not retain the superiority of response at all levels of severity shown in the original study. Among endogenous patients, the superiority of amitriptyline was maintained only for the "old" group. Hoenig and Visram (1964), found that endogenous patients over 60 did slightly better on amitriptyline than on imipramine.

Comparison of Responder with Non-Responder Groups

The non-responder group was compared with all others on the initial symptom scores of the Hamilton rating scale. The non-responders showed a significantly higher average symptom score ($p < \cdot 01$), a significantly greater loss of insight ($p < \cdot 01$), were more agitated ($p < \cdot 05$), and exhibited more guilt feelings ($p < \cdot 05$).

Prognostic Considerations

A number of variables were assessed to determine whether they were of prognostic value for either drug, in terms of response without re-admission, and in some cases in terms of response without recurrence at 18 months.

(1) *Age and Severity*

Neither of these factors was found to be of prognostic significance for either drug.

(2) *Type of Illness*

With imipramine, a significantly greater number ($p < \cdot 05$) of reactive patients responded without re-admission as compared to patients in the endogenous category.

There are conflicting reports on the influence of age on prognosis. Kiloh *et al.* (1962), found that for response to imipramine, without recurrence over six months patients over 40 years of age had a better prognosis. Both Angst (1961), and Andersen and Kristiansen (1959) found that with imipramine there was no definite relation between immediate response and age, whilst on the other hand Freyhan (1960) found it less useful in the old age group. Skarbek (1963) found amitriptyline to give a good response in chronic depressives over the age of 45 years. Our own study failed to confirm the hypothesis that the iminodibenzyl derivatives are to be preferred with endogenous depression. Andersen and Kristiansen (1959) found that imipramine was most effective in the mild or moderate cases, as did Kiloh *et al.* (1962), whilst Abraham *et al.* (1963) found a slight but just significant tendency for the more severely depressed to show a greater degree of improvement.

(3) *Clinical Picture*

The mean initial scores on the Hamilton rating scale for the responders without re-admissions in each drug group were compared with the mean initial scores of all other patients.

For imipramine, the responders without re-admission were significantly less depressed in mood ($p < \cdot 05$), had less reduction in work and interests ($p < \cdot 05$) and were less agitated ($p < \cdot 05$). For amitriptyline, they had a lower total mean score and less suicidal ideas and tendencies ($p < \cdot 05$).

Angst (1961; 1963), has summarized previous findings and re-affirmed the value of amitriptyline in the agitated and of imipramine in the inhibited forms. Robin and Langley (1964), whilst not finding imipramine superior to placebo in a group of depressives, did find that in regard to work and interest the imipramine-treated patients did significantly better than the placebo ones. Our findings partially confirm these different responses, as they show the poor long-term response to imipramine by patients with agitation. However, Fleminger and Groden (1962) did not find that agitation correlated with imipramine response, and Hordern *et al.* (1963), whilst they found that agitation gave a negative correlation with response to imipramine, did not find that it correlated with amitriptyline response. Skarbek (1963), comparing amitriptyline and placebo effect, found the former to be of value both for patients with agitation and those with retardation, whilst Sandifer *et al.* (1965) found that both drugs were just as effective on agitated patients.

(4) *Psychiatric History*

For each drug group, the responders without re-admission were compared with all others on four aspects of their psychiatric history.

The following were not found to be of prognostic significance: the number of previous hospitalizations, the suddenness of onset of the first illness and the speed of onset of the current illness. But the amitriptyline responders without re-admission were found to have a significantly shorter number of years since their first hospitalization ($p < \cdot 02$).

Angst (1963), found that for both drugs as the number of previous phases increased resistance to therapy increased.

Reliability of Diagnosis

Thirty-eight patients were re-admitted within 18 months; of these, four were then given a diagnosis of schizophrenia. Figures from other studies vary widely. Clark and Mallett (1963) found that of 86 depressives followed up after three years, 20 per cent. required re-admission, and one third of these were then diagnosed as schizophrenia. Astrup *et al.* (1959) stated that, according to the literature, between 3 and 8·5 per cent. of patients require diagnostic revision. They found that, of 70 cases of pure manic-depressive illness followed up for many years, none had their diagnosis changed; but that, of 26 cases who had revealed some schizophrenic symptoms, 13 on follow-up were regarded as schizophrenics.

Delusions

A comparison of the efficacy of the two drugs was made, including only patients with no delusions in their original illness. This was necessary because 17 deluded patients had been placed on imipramine and only 10 had been on amitriptyline, and the presence of delusions had been shown in the original study to be associated with a poor prognosis (Hordern *et al.*, 1963). In fact, their figures showed the difference in efficacy of the drugs on non-deluded patients alone to be relatively small after 4 to 6 weeks of treatment. The results after 18 months follow-up were consistent with this earlier finding, and in terms of response without recurrence and response without re-admission there was no significant difference between the drugs. Of non-deluded patients on amitriptyline, 21 of 48 (44 per cent.) responded without recurrence and 30 (63 per cent.) responded without re-admission. For imipramine, the corresponding figures were 17 of 46 (37 per cent.) without recurrence and 26 (56 per cent.) without re-admission.

Discussion

There has been some discussion as to whether drug maintenance therapy reduces recur-

rence and re-admission rates (Polonio, 1961; Ayd, 1961). The results from the present study do not allow of any definite conclusion. However, the recurrence and re-admission rates over the first six months after discharge when drug therapy was continued are not significantly different from the rates for the next two six-month periods (Table III and Fig. 2). Either maintenance therapy has no significant influence on these rates, or they are naturally higher for the first six months after a depressive illness requiring hospitalization. If the latter explanation is valid, maintenance therapy reduced the re-admission and recurrence rates to the extent that there were no significant differences for the rates for the first six months, when compared with the subsequent two six-month periods, not only for the responder group, but also for the total patient group (Tables IV and V, Fig. 4).

Most of the literature in the last two decades dealing with the assessment of various treatment modalities has been restricted to short term prognostic studies. Not only have follow-up periods been short, but terms (e.g. relapse, recurrence) have seldom been defined, and descriptions of methodology have been inadequate. Often patients within the one study have been followed up for varying periods of time, making comparisons difficult. A greater emphasis on long-term investigations is now necessary to extend our knowledge.

One of the major failures in psychiatry has been the inability to establish universally acceptable classificatory systems. Indeed, there are those who would reject the whole concept of classification, particularly on the grounds of the lack of validity and reliability (Kessell, 1964). The classification of the depressive states has always caused controversy, and for many years there has been much discussion on the validity of the concepts of reactive (exogenous, neurotic), and endogenous depression. Mapother (1926), Lewis (1934), Garmany (1958) and others have denied that there is a qualitative difference between them, believing either that the reactive and endogenous categories are facets of the same condition or that the difference is only quantitative, whilst other authors have affirmed the independence of these categories as separate entities (Astrup *et al.*, 1959; Kiloh and Garside, 1963; Hobson, 1953; Busfield *et al.*, 1962; Kline, 1961).

One of the arguments for a qualitative dif ence has utilized the results of the action of different therapies. E.C.T. has been found be most useful for patients classified as en geneous (Roberts, 1959; Rose, 1963; Thon 1954), the M.A.O. inhibitors for the reac and atypical categories (West and Dally, 19 Sargant, 1961), and the iminodibenzyl de atives for the endogenous category (Kiloh *et* 1962; Layberg and Denmark, 1959; Friedn *et al.*, 1961). But at times the reverse of usual prognostic criteria have been found. T iminodibenzyl derivatives have been found tc effective in reactive depression (Oltman Friedman, 1961; Browne *et al.*, 1963; Abrah *et al.*, 1963), and although studies of symptoms most responsive to E.C.T. have sho they approximate those of endogenous dep sion, nevertheless it is only an approximat (Kiloh and Garside, 1963; Hobson, 1953).

These anomalies have been considered Pare *et al.* (1962), who say: "it is suggested t the majority of patients with depressive illn may well have a genetic predisposition, a though in some cases this may only be slig it would determine the type of biochemi abnormality precipitated by the predomin exogenous factors", and " . . . the response c particular type of antidepressant may depe more on the fundamental biochemical abn mality of the illness than on the more superfi clinical presentation". Not only the response antidepressants, but also that to E.C.T. m depend fundamentally on a biochemical normality. Patients responding to E.C.T. fail fit into the reactive-endogenous dichotor and there is an overlap of action with a depressant drugs (Angst, 1961). Goldner (19 used imipramine and the M.A.O. inhibitors the treatment of minor criminal sexual co pulsions, and concluded, "Such (compulsi reactions appear to have at least two ma biochemical patterns, namely, those that controlled by imipramine, and those by am oxidase regulators. One only of these two ty of agents tends to be of help to a given patien Kalow, in his book *Pharmacogenetics* (196 discusses examples of discontinuous variation

response to drugs, variations usually related to monofactorial inheritance. He gives as one example the individual variations in the rate of acetylation of isoniazid in the body, and it is suggested that the ability to metabolize isoniazid is controlled by an autosomal dominant gene; that is, there are genetically determined slow and fast inactivators of this drug.

It may then be hypothesized that drug responses (and the lack of them) are determined primarily by differing biochemical configurations for the depressive states, and these genetico-biochemical entities would vary as to the amount and form of exogenous precipitation required to produce the clinical state. The final clinical manifestations would depend on the interactions of the constitutional bases (biological and psychological) and exogenous stresses (physical and psychological). Such a hypothesis explains the failure to correlate both the reactive-endogenous dichotomy and target symptoms with drug response. The clinical picture, being the "final common pathway", allows similar symptom-clusters to be the expression of dissimilar genetico-biochemical configurations. This may explain why for instance, an "endogenous" type treatment may produce a response in an apparently "reactive" depression.

This study provides some supporting evidence. There was no significant differences in the recurrence rates of the endogenous and reactive categories (Table IV and V), but the endogenous patients had higher re-admission rates. These findings suggest that, for recurrence and re-admission, there are no qualitative differences between these categories, only that the endogenous form is more clinically severe. This was also supported by the fact that the endogenous patients had a significantly larger number who scored over 40 on the rating scale before treatment. It is consistent with the need to look beyond the reactive-endogenous division that recurrence was found to be independent of this division, and of severity, while re-admissions were correlated with severity.

The failure of research so far to establish adequate prognostic criteria within the framework of the reactive-endogenous dichotomy may in part to be due to the clinician himself as a variable in the research. There are differing theoretical orientations, different clinical training programmes and individual socio-cultural background to be considered. These are unlikely to be the whole answer, and it has been shown in recent years that diagnostic reliability can be high (Kreitman *et al.*, 1961). Even the use of well defined aspects of personal history does not avoid conflicting results; whilst Angst (1963) found that as the number of previous depressive phases increases so does resistance to the drugs, our study showed no significant correlation between the number of previous hospitalizations and drug efficacy.

Another possible explanation for the failure to establish adequate prognostic criteria is the failure to take into account, as has been suggested, the fundamental psycho-biological nature of the depressive states. If there are genetico-biochemical differences paralleled by differences in therapeutic response, the clinical picture will be the expression not only of these biochemical differences, but also of personal and socio-cultural factors. We would therefore need to look for psycho-biological correlates rather than symptom correlates. The assessment of target symptoms seems to have little value for prognosis.

Summary

116 out of 137 depressed patients involved in a previous drug trial were followed up 18 months after hospitalization.

Recurrence and re-admission rates were determined for the original amitriptyline and imipramine responders and non-responders; the longitudinal efficacy of the drugs were assessed, and prognostic factors for response without recurrence and re-admission were determined.

It was shown that the reactive and endogenous groups had similar recurrence rates, and that the endogenous patients had higher re-admission rates. Support was given for a quantitative difference only between reactive and endogenous depression, and the importance of constitutional factors in both types was discussed.

No firm conclusion could be drawn as to the value of drug maintenance therapy in preventing relapse. The drug responders included

reactive patients with high recurrence and low re-admission rates, and endogenous patients with moderately high recurrence and re-admission rates. The drug non-responders included reactive patients with low recurrence and re-admission rates, and endogenous patients with high recurrence and re-admission rates. The drug non-responders also had a higher average symptom score, a greater loss of insight and greater agitation, and exhibited more guilt feelings.

After 18 months, amitriptyline was no longer significantly superior to imipramine, except for the endogenous depressives in the 50 to 70 years age group. With imipramine, the best 18 months prognosis was for reactive patients, who showed less depressed mood, less reduction of work and interests and less agitation. For amitriptyline, the best prognosis was for those with less suicidal proclivities and a lower initial score on the rating scale and who had a relatively small number of years since their first hospitalization.

The results were generally consistent with hypotheses recently advanced concerning the biochemical aspects of depression and of response to different drug treatments, and it was suggested that in looking for prognostic indicators more attention should be given to possible psycho-biological correlates of depression.

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